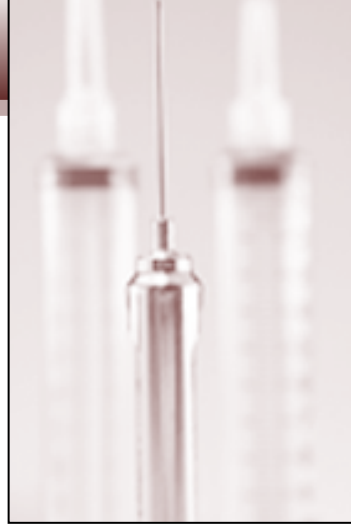

Chapter 3

Genomics and Vaccine Safety: Research for Future Practice

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Need for Vaccine Safety Research

Each year, more than four million children are born in the United States. Parents naturally want to protect their children as much as possible from disease and illness. One of the most effective ways to accomplish this goal is for children to receive immunizations according to the recommended vaccination schedule (1). During 2001, almost 80% of children aged 19-35 months of age living in the United States received **vaccine** coverage for DTP/DT/DtaP, poliovirus, and measles.

Vaccines
Preparations of killed or modified bacteria or viruses meant to stimulate an immune response to ward off future disease.

Autism
A childhood disorder of unknown etiology characterized primarily by profound deficits in communication and social interactions.

Thimerosal
A mercury-containing organic compound that was widely used until recently as a preservative in vaccines.

Throughout the United States and other countries, however, vaccine safety concerns have increased. Popular media, including parenting magazines, have discussed purported associations of vaccines with negative health effects, such as **autism** and inflammatory bowel disease, as well as the potential negative health effects of vaccine preservatives (e.g., **thimerosal**) on neurological development. These negative reports are often widely believed, despite the lack of solid evidence. Both public health professionals and physicians are frequently called upon to assure parents that a relationship between vaccinations and neurodevelopment disorders has not been established, although due to insufficient data, the absence of such an association has not been confirmed either. Whether certain people may be at increased risk for adverse effects from vaccination because of an underlying health condition or because of their individual genetic make-up is an important area for research.

Current Vaccine Safety Research at CDC

The Centers for Disease Control and Prevention (CDC) has three major components for vaccine safety monitoring and research:

- *Vaccine Adverse Events Reporting System (VAERS)*. *VAERS* is a nationwide passive reporting system for voluntary reports of adverse events that are suspected of being related in some way to vaccination.

- *Vaccine Safety Datalink project (VSD)*. *VSD* is a large collaborative project that links data from eight managed care organizations (MCOs) in the

United States, covering approximately 3-4% of the U.S. population (2,3). The automated databases from these MCOs can be used to link vaccinations to outcomes, including subsequent visits for symptoms or illnesses that are evaluated in outpatient settings, emergency departments, or hospitals. A particularly strong component of VSD is its coverage of millions of enrolled subjects, allowing for the study of rare events that might follow immunization. Typically, VSD contains information necessary for rigorous epidemiologic studies, including numbers of vaccine doses administered, comparison groups, and individual-level data on potentially confounding variables.

- *Clinical Immunization Safety Assessment (CISA) network*. *CISA* is a new initiative created to fill the need for individualized evaluations of patients with specific vaccine-associated adverse events or with specific immunization-related needs. CISA is a network of clinical academic centers that work in partnership with CDC to improve scientific understanding of vaccine safety at the individual patient level, providing clinical expertise in evaluating and treating adverse events following immunization.

Integrating Genomics Into Vaccine Safety Studies

Currently, both VSD and CISA are working toward integrating genomics into studies of vaccine safety. Two examples of these studies are as follows:

Myopericarditis
Inflammation of the heart muscle and the membrane surrounding it.

- *CISA study of myopericarditis*. The primary goal of this study is to define prospectively the incidence of **myopericarditis** following vaccination in 600 enrolled subjects receiving smallpox vaccination and 200 persons receiving influenza vaccination. The study will also assess inflammatory markers (cytokines and other immune factors) in vaccinees who develop clinical or subclinical myopericarditis in comparison with asymptomatic vaccinees (controls).

  In collaboration with the National Institutes of Health (NIH), funding for this study has been substantially increased to collect, transport, and store DNA, RNA, and blood mononuclear cells from all smallpox vaccines and controls for genetic analyses and detailed evaluation of the immune response in cases and controls.

Rheumatoid arthritis (RA)
A chronic disease characterized by joint inflammation.

- *VSD study of rheumatoid arthritis*. VSD includes an ongoing genetic substudy of **rheumatoid arthritis (RA)** following hepatitis B vaccination (HBV). The goal of this study is to determine whether a genetic predisposition to developing RA exists following HBV. Interactions between genes and other genetic polymorphisms and HBV in the development of RA will be examined in a case-only study of RA cases from CDC's

VSD project. The case-only study design is highly efficient, because the distribution of HLA (human leukocyte antigen) gene variants in the population is not expected to vary with HBV exposure.

The impetus for this study originated with reports to VAERS between 1991 and 1998 of 39 persons with RA following HBV vaccination. Data analysis suggested a twofold increase in the rate of possible RA in HBV recipients compared with the rate in influenza vaccine or pneumococcal polysaccharide vaccine (PPV) recipients. Among RA cases reported to VAERS, the mean time from vaccination to onset of symptoms was 3.6 days (range: 0–9 days). The mean age of the reported RA cases was 41 years (range: 18–58 years). Other non-RA rheumatic conditions were also reported, including systemic lupus erythematosus (SLE), gout, and reactive arthritis. Despite the limitations of a passive reporting system, such as VAERS, this analysis suggests an increased rate of RA following HBV compared with PPV or influenza vaccination.

These data prompted the VSD to develop a protocol to determine whether HBV increases the risk of chronic joint disease. All persons aged 15 to 59 years with continuous MCO membership from January 1, 1995 to December 30, 1999 were eligible, and those with an automated record diagnosis of RA were selected for further medical record review. RA cases were confirmed by using the 1987 American College of Rheumatology criteria and a rheumatologist's chart review. To date, blood samples have been collected from more than 300 subjects with confirmed or likely RA for evaluation of HLA status. In addition, a study will be conducted on a number of polymorphisms recently found to be risk factors for developing RA, such as the *PTPN22* SNP as well as other **SNPs** in this gene/region.

SNPs
Single nucleotide polymorphisms.

The Future of Genomics and Vaccine Safety

The study of the genomics of vaccine safety is in its infancy. The creation and maintenance of large collaborative projects are needed to allow collection of the necessary information (including DNA) from large numbers of people. In the future, a greater understanding of population-wide genetic variation will allow the delivery of safer and more efficacious vaccines, and may allow for the personalized delivery of specific vaccines.

References

1. Centers for Disease Control and Prevention. Recommended childhood and adolescent immunization schedule–United States, 2005. MMWR [online] 2005;53 (Nos. 51&52):Q1–Q3 [cited 2005 Aug 11]. Available from URL: *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5351-Immunizationa1.htm*.

2. Chen RT, Glasser JW, Rhodes PH, Davis RL, Thompson RS, Mullooly JP, et al. Vaccine Safety Datalink Project: A new tool for improving vaccine safety monitoring in the United States. Pediatrics 1997;99:765-73.

3. Chen RT, DeStefano F, Davis RL, Jackson LA, Thompson RS, Mullooly JP, et al., and the Vaccine Safety Datalink Team. The Vaccine Safety Datalink: immunization research in health maintenance organizations in the USA. Bulletin of the World Health Organization 2000;78(2):186-94.